



# UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE  
United States Patent and Trademark Office  
Address: COMMISSIONER FOR PATENTS  
P.O. Box 1450  
Alexandria, Virginia 22313-1450  
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/410,539	03/24/1995	MATTHEW B. WHEELER	7823/5	2654

757 7590 06/17/2003

BRINKS HOFER GILSON & LIONE  
P.O. BOX 10395  
CHICAGO, IL 60611

EXAMINER

TON, THAIAN N

ART UNIT	PAPER NUMBER
----------	--------------

1632

34

DATE MAILED: 06/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

Application No.

08/410,539

Applicant(s)

WHEELER, MATTHEW B.

Examiner

Thai-An N. Ton

Art Unit

1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☐ Responsive to communication(s) filed on \_\_\_\_.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-6,9-12,14-20 and 22-77 is/are pending in the application.
- 4a) Of the above claim(s) 14-20 and 22-77 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-6,9-12 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.  
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

### Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All b) ☐ Some \* c) ☐ None of:  
1. ☐ Certified copies of the priority documents have been received.  
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_.  
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).  
\* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).  
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

### Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_ 6) ☐ Other: \_\_\_\_

## DETAILED ACTION

The Examiner of record has now changed. The Examiner is now Thaian N. Ton of Art Unit 1632.

Claims 1-6, 9-12, 14-20 and 22-77 are currently pending. Claims 14-20 and 22-77 are withdrawn from consideration; claims 14 and 22-77 are directed to non-elected claims. Claims 1-6, 9-12 are under current examination.

### *Decision on Appeal*

The decision on the appeal under 35 U.S.C. §134 from the Examiner's final rejection of claims 1-6, 9-12 and 15-20 was mailed 1/22/03, Paper No. 33. The Board of Patent Appeals and Interferences affirm the rejections for double-patenting and affirm-in-part and reverse-in-part the rejection for non-enablement. Particularly, the rejection of claims 1-6 and 9-12 is reversed and the rejection of claims 15-20 is affirmed. Claims 15-20 have been reversed and are withdrawn from further prosecution because they are not subject to further prosecution. Claims 1-6 and 9-12 are under current examination. A new action on the merits appears below.

### *Double Patenting*

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

Art Unit: 1632

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

The prior rejection of claims 1-6 and 9-12 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6, 9-12 of U.S. Patent No. 5,942,435 [formerly U.S. Application No. 08/473,030] is *maintained*. Although the conflicting claims are not identical, they are not patentably distinct from each other because the methods recite essentially the same method steps, and the species "swine" of the patented claims anticipates the genus "ungulate" of the instant claims. The Board of Appeals notes that the Appellant has not disputed the merits of these rejections and has agreed to file a terminal disclaimer to overcome them. See Paper No. 21, filed 11/9/98, p. 2. The terminal disclaimer is now required.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 3 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was

Art Unit: 1632

not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claim is directed to methods of making a chimeric ungulate comprising the introduction of a totipotent ungulate embryonic stem cell that has a first genetic complement into a recipient embryo of the same species as the embryonic stem cell, said recipient having a second genetic complement, to form a chimeric ungulate embryo, and placing the chimeric ungulate embryo in an environment suitable for the complement of development to form a chimeric ungulate.

The enablement rejection pertains to the predictability of producing or obtaining totipotent embryonic stem cells. The Board found that claims 15-20, drawn to methods of making ES cells, were not enabled. They state:

*In this case, the examiner has provided a reasonable explanation, supported by evidence, of why the full scope of claim 15 is not enabled by the guidance provided in the specification. The examiner has cited numerous prior art references supporting his position that isolating embryonic stem cells is a highly unpredictable endeavor. See p. 10, 2<sup>nd</sup> full ¶.*

As such, the Decision, as clearly set forth by the Board, is that with regard to claim 3, the isolation and obtaining of totipotent stem cells is a highly unpredictable art. The Board of Appeals considered only claim 1, and because claim 3 is contrary to the reversal, the rejection of claim 3, under 112, 1<sup>st</sup> ¶, for enablement, is

Art Unit: 1632

maintained. In the prior Office actions, the Examiner has provided several references to support that the state of the art of ES cell technology is unpredictable; and the Board clearly affirms that the production and availability of totipotent ES cells is not enabled. For example, in the Office action mailed 3/17/97, Paper No. 14, page 3, cites the differences among the embryonic development of mammalian species [Cruz *et al.*, Bazer *et al.*, Piedrahita *et al.*]. In particular, it states:

In the instant application, the specification has been amended to allege that the methods which were shown to be effective for swine are also effective for other ungulate species. There is reason to doubt this assertion, given the unpredictable nature of the art. Mammalian species differ in their embryonic development. Differences among species are acknowledged by Applicant [specification, p. 5]. Cruz *et al.* [A20] list some of the differences in early embryonic development among swine, oxen, horses, goats and sheep [*e.g.*, Table 1]. Bazer *et al.* [A11] also provide an overview of differences among ungulate species [see entire document]. Piedrahita *et al.* [A52] observed that porcine and ovine embryos responded differently to the same treatments. Conditions which allowed production of porcine ES-like cell lines did not allow development of ovine ES-like cell lines [*e.g.*, Table 1]. Piedrahita *et al.* state, "Ovine intact embryos and isolated ICM behaved differently than porcine embryos" [p. 888]. Furthermore, those skilled in the art recognize that not all "ES-like" cells are "true" ES cells, *i.e.*, totipotent cells capable of contributing to the germ line of

Art Unit: 1632

chimeric animals. The specification acknowledges the need to "validate" ES cells [p. 10].

The Examiner provides further evidence to support the unpredictability of ES cell technology in the final Office action mailed 1/9/98, Paper No. 17, pages 3-4, which states:

Applicant argues that the claimed methods have been used to produce sheep ES cells, citing the Wheeler declaration. This argument is not persuasive because ES-like cells disclosed in the declaration do not meet an important art-accepted criterion of an ES cell, the ability to be incorporated into all cell types of an organism, particularly the germ line. For example, Nichols *et al.* [A47] state that "[e]mbryonic stem cells ... retain the ability to participate in normal embryonic development and, following reintroduction to the blastocyst, they generate chimæric animals that are mosaic in *all* their tissues. Mosaicism extends to the germ cell lineage and *ES cells can contribute fully functional gametes.*" [p. 1341, 1<sup>st</sup> ¶, emphasis added]. Applicant has demonstrated that the disclosed sheep ES-like cells have an appearance similar to swine ES cells, but not that they can be used to generate chimeric sheep and contribute fully functional gametes. Additional examples from the art are cited below. Kollias *et al.* [A37] state that, "[a]fter reintroduction into blastocysts, [ES cells] can contribute to all the tissues of the mice derived from the reimplanted blastocysts, *including germ line cells.*" [p. 92, emphasis added]. Wurst *et al.* [A73] state that, "ES cells resemble in many aspects ICM cells *especially in their ability to contribute to all tissues in chimeras*" [p.33].

Clark *et al.* [A18], discussing the isolation of putative swine ES cell lines, state that "[t]he isolation of ES cells from domestic livestock has not yet been conclusively demonstrated ... [P]ig cells have been ... used in blastocyst injection experiments. Preliminary results indicate ... that these cells can contribute to tissues in the developing animal. *Demonstration that these cells are able to contribute to the germ line is awaited*" [p. 250, 2<sup>nd</sup> full ¶; emphasis added].

The unpredictability of the ES cell technology is further supported by post-filing art. For example, Moreadith *et al.* [J. Mol. Med., 1997, p. 214, *Summary*] note that the state of the art is such that ES cell technology is generally limited to the mouse system at present, and that only "putative" ES cells exist for other species. Note that "putative" ES cells lack a demonstration of the cell to give rise to germline tissue or the whole animal, a demonstration which is an art-recognized property of ES cells. Such a demonstration has not been provided by the specification or the prior or post-filing art with regard to the generation of any species of animal ES cells, other than the mouse, which can give rise to the germline tissue of a developing animal. In addition, prior to the time of filing, Mullins *et al.* (*Journal of Clinical Investigation*, 1996) report that "although to date chimeric animals have been generated from several species including the pig, in no species other than the mouse has germline transmission of an ES cell been successfully demonstrated." (page 1558, column 2, first paragraph). As the claims are drawn to methods



Art Unit: 1632

involving the manipulation of *totipotent* ungulate embryonic stem cells, the state of the art supports that it would have been unpredictable to isolate and produce such cells.

The unpredictability in the state of the art is further supported by Pera *et al.* [Journal of Cell Science 113: 5-10 (2000)] who present the generic criteria for pluripotent ES or EG cells [see p. 6, 2<sup>nd</sup> column] and state that, "Thus far, only mouse EG or ES cells meet these generic criteria. Primate ES cells meet the first three of the four criteria, but not the last. Numerous other candidate mammalian ES cells have been described over the years in domestic and laboratory species, but only in the mouse have all criteria been met rigorously." [See p. 6, 2<sup>nd</sup> column, last paragraph].

Accordingly, in view of the specification's lack of teaching or guidance with regard to totipotent ungulate stem cells, the unpredictable state of the art of ES cell technology, the amount of experimentation necessary to produce totipotent ungulate ES cells, it would have required undue experimentation for one of skill in the art to make and/or use the claimed invention.

### *Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

Art Unit: 1632

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 4, 5 and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Evans *et al.* [WO 90/03432, published 5 April 1990, cited in Applicants' Information Disclosure Statement, filed 6/4/1996, Paper No. 10].

The claims are directed to methods for making a chimeric ungulate comprising (a) introducing a cultured ungulate embryonic stem cell that has a first genetic complement into a recipient embryo of the same species as the embryonic stem cell, said recipient having a second genetic complement, to form a chimeric ungulate embryo; and (b) placing the chimeric ungulate embryo in an environment suitable for the completion of development to form a chimeric ungulate, wherein the stem cell is pluripotent [claim 2], wherein the stem cell is introduced at a pre-implantation stage [claim 4], wherein the pre-implantation stage is the blastocyst stage [claim 5], wherein the first genetic complement is different from the second genetic complement [claim 9], wherein the first genetic complement comprises an exogenous nucleotide sequence stably integrated into the genetic complement of the embryonic stem cell [claim 10].

Evans teaches methods of producing pluripotent ES cells from ungulates, such as porcine and bovine species. See *Abstract*. Evans discusses the methods for introducing genetic alterations into a mammal which can lead somatic genetic mosaicism. See p. 4, 2<sup>nd</sup> ¶. Particularly, Evans teach the isolation of pluripotent ES cells from ungulate embryos [bovine and porcine]. See pp. 8-11. They further

discuss utilizing the ES cells for the production of embryos carrying particular genetic backgrounds or specific mutations. See p. 11, 4<sup>th</sup> ¶. They state that:

*Furthermore, the invention can provide for the use of such cells to repopulate an embryo of the same species thus giving rise to a chimæric animal, particularly a chimæric animal in which some or all the germ cells are derived from the tissue-culture cells; for example a chimæric animal in which some or all of the germ cells are derived from the tissue-culture cells where the embryonic stem cells have been genetically modified or selected for genetic modification in culture.* See p. 12, 1<sup>st</sup> ¶.

Evans teach that the stem cells that are produced from bovine blastocysts can be introduced into a host blastocyst by, for example, micromanipulation, and then the resulting blastocyst can then be introduced into the uterus of a pseudopregnant foster mother, where it can develop into a chimeric animal. They further teach that prior to introduction to the host blastocyst, the ES cells can be genetically manipulated to express a gene of interest. See pp. 14-15 and p. 19, 2<sup>nd</sup> ¶. Evans teach methods which can be used to establish ES cell cultures from porcine embryos, that the pluripotency of these cells was verified by differentiation into embryoid bodies. See pp. 21-23.

Note that the specification defines a *genetic complement* as, "[A]ll genes present, or may designate a particular gene or genes of interest. Therefore, a complement may be "different" because it has a different allele of a gene, or a different gene or genes and may be from a different species." See pp. 11-12,

Art Unit: 1632

bridging ¶. As such, in view of the teachings of the specification, the surrogate mother would have a different genetic complement than that of the blastocyst, as they would be expected to have different alleles of a gene, for example.

Accordingly, Evans anticipates the claimed invention.

*Claim Rejections - 35 USC § 102/103*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1, 2, 4, 5 and 6 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Kashiwazaki *et al.* [The Veterinary Record, 130(9):186-187 (1992), cited in Office action mailed 3/17/97, Paper No.14].

The claims are directed to methods for making a chimeric ungulate comprising (a) introducing a cultured ungulate embryonic stem cell that has a first

genetic complement into a recipient embryo of the same species as the embryonic stem cell, said recipient having a second genetic complement, to form a chimeric ungulate embryo; and (b) placing the chimeric ungulate embryo in an environment suitable for the completion of development to form a chimeric ungulate, wherein the embryonic stem cell is derived from a first breed of ungulate and the recipient embryo is derived from a second breed of the same species as the first breed.

Kashiwazaki teach methods of producing chimeric pigs. They teach that blastocysts produced from the mating of Large White cross Large White, or Landrace cross Large White pigs [white in coat color] were used as the donor embryos. See p. 186, 2<sup>nd</sup> column, 2<sup>nd</sup> ¶ of the reference. Host blastocysts, which were brown in coat color, were collected from Duroc females. Dissociated inner cell mass cells were introduced into the blastocoel of the donor blastocysts. The resulting embryos were then transferred to recipient gilts, and two of the three recipients became pregnant and delivered a total of 11 piglets. One offspring was chimeric, and another had a complete white coat color, indicating a large contribution from the injected inner cell mass cells. It was found that the porcine inner cell mass cells could contribute efficiently to the development of pigs when injected into blastocysts. See p. 187, 1<sup>st</sup> ¶.

Accordingly, it would have been obvious for one of skill in the art to modify the methods of Kashiwazaki and use ES cells in methods of making chimeric pigs.

Art Unit: 1632

One of skill in the art would have been sufficiently motivated to make such a modification because an ES cell is a culture of inner cell mass cells.

Thus the claimed invention as a whole was clearly *prima facie* obvious at the time the claimed invention was made especially in the absence of sufficient, clear and convincing evidence to the contrary.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1, 9-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Evans et al. [WO 90/03432, published 5 April 1990] when taken with Clark *et al.* [Genome 31(2):950-955 (1989)].

The claims are directed to methods for making a chimeric ungulate comprising (a) introducing a cultured ungulate embryonic stem cell that has a first genetic complement into a recipient embryo of the same species as the embryonic stem cell, said recipient having a second genetic complement, to form a chimeric ungulate embryo; and (b) placing the chimeric ungulate embryo in an environment suitable for the completion of development to form a chimeric ungulate, wherein the

first genetic complement is different from the second genetic complement [claim 9], wherein the first genetic complement is an exogenous nucleotide sequence stably integrated into the genetic complement of the ES cell [claim 10], wherein the genetic complement is human Factor IX, which is recoverable from the chimeric ungulate [claim 11], wherein the genetic complement comprises a nucleotide sequence encoding a protein selected from the group consisting of human blood proteins, human hormones, human growth factors, human cytokines, human enzymes, human hormone receptors, human binding proteins, antigens, translation factors, transcription factors, onco-proteins, proto-oncoproteins, human milk proteins, and human muscle proteins [claim 12].

Evans teaches methods of producing pluripotent ES cells from ungulates, such as porcine and bovine species. See *Abstract*. Evans discusses the methods for introducing genetic alterations into a mammal which can lead somatic genetic mosaicism. See p. 4, 2<sup>nd</sup> ¶. Particularly, Evans teach the isolation of pluripotent ES cells from ungulate embryos [bovine and porcine]. See pp. 8-11. They further discuss utilizing the ES cells for the production of embryos carrying particular genetic backgrounds or specific mutations. See p. 11, 4<sup>th</sup> ¶. They state that:

*Furthermore, the invention can provide for the use of such cells to repopulate an embryo of the same species thus giving rise to a chimæric animal, particularly a chimæric animal in which some or all the germ cells are derived from the tissue-culture cells; for example a chimæric animal in which some or all of the germ cells are derived from the tissue-culture cells where the*

Art Unit: 1632

*embryonic stem cells have been genetically modified or selected for genetic modification in culture.* See p. 12, 1<sup>st</sup> ¶.

Evans teach that the stem cells that are produced from bovine blastocysts can be introduced into a host blastocyst by, for example, micromanipulation, and then the resulting blastocyst can then be introduced into the uterus of a pseudopregnant foster mother, where it can develop into a chimeric animal. They further teach that prior to introduction to the host blastocyst, the ES cells can be genetically manipulated to express a gene of interest, "It can allow the use of stem cells genetically transformed in such a way as to introduce a novel protein production in a specific part (*e.g.*, the mammary gland, the liver) of a subsequently derived chimæric animal." See p. 12, 1<sup>st</sup> full ¶.

Evans do not teach that the first genetic comprises an exogenous nucleotide sequence stably integrated into the genetic complement of the ES cell, such as human Factor IX. However, prior to the filing of the claimed invention, Clark *et al.* [Genome 31(2):950-955 (1989)] teach methods of targeting expression of DNA sequences of interest to the mammary gland. They particularly teach the construction of a fusion gene comprising beta-lactoglobulin sequences and sequences encoding human factor IX. See p. 952, 2<sup>nd</sup> column, *Fusion constructs*. These constructs were used in gene transfer in sheep by the pronuclear injection of ovine oocytes. See Table 1. After microinjection, 307 sheep eggs were transferred to recipient ewes and 52 lambs were born, 4 of which were transgenic. See Figure 4



and p. 953, 2<sup>nd</sup> column, 2<sup>nd</sup> ¶. During lactation, milk was collected from two of the transgenic females, and analyzed for the presence of Factor IX. Radioimmunoassays found that the animals secreted detectable levels of the protein in their milk. See p. 954, 1<sup>st</sup> column, 1<sup>st</sup> ¶.

Accordingly, in view of the combined teachings, it would have been obvious for one of ordinary skill in the art, to modify the methods of producing a chimeric ungulate expressing a gene of interest, as taught by Evans, by using a targeting construct encoding human factor IX, as taught by Clark, with a reasonable expectation of success. One of ordinary skill in the would have been sufficiently motivated to make such a modification as supported by Clark, who teach that the generation of genetically modified livestock who secrete proteins in their milk can be used to produce large quantities of medically important proteins, such as clotting factor IX. See *Abstract* and p. 951, 2<sup>nd</sup> column, 1<sup>st</sup> full ¶.

Thus the claimed invention as a whole was clearly *prima facie* obvious at the time the claimed invention was made especially in the absence of sufficient, clear and convincing evidence to the contrary.

Art Unit: 1632

*Conclusion*

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thái-An N. Ton whose telephone number is (703) 305-1019. The examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the examiner be unavailable, inquiries should be directed to Deborah Reynolds, Supervisory Primary Examiner of Art Unit 1632, at (703) 305-4051. Any administrative or procedural questions should be directed to William Phillips, Patent Analyst, at (703) 305-3482. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

TNT

Thái-An N. Ton  
Patent Examiner  
Group 1632

*Deborah Crouch*

DEBORAH CROUCH  
PRIMARY EXAMINER

GROUP 1800-1632